Journal of the Pediatric Infectious Diseases Society

BRIEF REPORT

Ethanol Lock Therapy for the Treatment of Intravenous Catheter Infections That Have Failed Standard Treatment

Roland Alexander Blackwood, Mohamad Issa, Kristin Klein, Rajen Mody, Michelle Willers, and Daniel Teitelbaum

University of Michigan, Ann Arbor, Michigan

This study used ethanol lock therapy (ELT) to treat intravenous catheter infections that had failed standard intravenous antimicrobial treatment. Of 15 patients enrolled, 13 were successfully treated with ELT. Twenty-one organisms were identified: 12 bacteria, 9 fungi. Eight of the 9 fungi were eradicated, and no patient became hemodynamically unstable on treatment.

Keywords. catheter infections; ethanol locks; fungal infections.

Patients requiring long-term central vascular access devices (CVAD) are at increased risk of developing catheter-related blood stream infections (CRBSIs). The incidence of CRBSIs in the literature is estimated to be between 16,000 and 500,000 annually in the United States [1], with the average admission costing between $3700 and $56,000 [2]. Ethanol lock therapy (ELT) has been used to decrease CRBSI incidence by as much as 90% in some studies [3–9], and it has been applied to the high-risk population of pediatric patients with IF to prevent CRBSI with excellent success [10, 11]. Significant methodological limitations are found in these ethanol lock studies, highlighting the need for further research to clarify the utility of ethanol locks in the management of CRBSI.

Catheter-related infections are most commonly caused by staphylococci (coagulase-negative and coagulase- positive), *Streptococcus viridans* species, *Enterococcus* species, and enteric Gram-negative organisms [12, 13]. Bacterial infections are usually managed with systemic antibiotics that last 7 to 21 days, and success for this treatment ranges between 60% and 91%, whereas fungal infections generally necessitate catheter removal due to a high rate of treatment failure.

An ethanol-lock salvage protocol was implemented for patients who (1) had failed standard treatment for their catheter infection and (2) were eligible to receive ethanol locks treatment in conjunction with the appropriate systemic antimicrobial, to clear catheter infection. In this article, the outcomes of this prospectively conducted study are presented.

METHODS

At the University of Michigan Mott's Children's Hospital, all infected CVAD that are clinically identified by the Centers for Disease Control and Prevention (CDC) guidelines undergo a standard attempt at antimicrobial therapy, if the patient is hemodynamically stable. In brief, the CDC guidelines define CVAD as a primary blood stream infection in a patient using a central access device within the 48-hour period before development of the infection and is not related to an infection at another site. Patients were eligible to be enrolled in the study if they failed standard treatment or had a fungus isolated, and the primary team determined that the catheter was to be replaced with a new catheter. Failure of standard treatment was defined as a persistence of positive blood cultures after 48-hour administration of appropriate intravenous antimicrobial treatment and antibiotic lock therapy when appropriate. Before subjects were assessed enrolled by the study team, the primary team had to obtain a mandatory Infectious Disease (ID) consult to independently assess (1) whether central access was required and (2) the appropriateness of attempting to salvage the catheter. Eligibility of the patient was assessed by the ELT study only after ID approval. The study was approved by the institutional review board.

The ETL protocol has been described previously [14]. In brief, the volume of the catheter lumen was measured for each individual patient to facilitate appropriate ethanol lock volume before the instillation of that volume of heparin-free 70% ethanol into the catheter, as described in previous reports [14, 15]. Ethanol locks were prepared utilizing sterile technique in the pharmacy by placing 7.5 mL sterile water and 18.75 mL 98% dehydrated alcohol into a 25 mL evacuated bag to achieve a final concentration of 70% ethanol [11]. A minimum dwell time of 2 hours and a maximum dwell time of 24 hours was set in accordance to our institution's guidelines regarding sterile compounding of injectable products. Dwell duration was adjusted for each patient to minimize catheter access and to avoid conflicts with other patient care requirements. At the completion

Received 25 March 2015; accepted 13 August 2015.

Correspondence: R. A. Blackwood, MD, PhD, Associate Professor, University of Michigan, 1500 East Medical Center Drive, D5101 Medical Professional Building, SPC 5718, Ann Arbor, Michigan 48109–5718 (rab@umich.edu).

Journal of the Pediatric Infectious Diseases Society 2017;6(1):94–7

DOI: 10.1093/jpids/piv060

of the dwell, the ethanol lock solution was removed from the catheter and discarded. After a minimum of 72 hours after the completion of ELT, a repeat blood culture was obtained. A negative culture was considered a treatment success.

Ethanol lock therapy was initiated after consent for both the clinical and research components of the ELT. Ethanol locks were administered once every 24 hours for a total of 14 days after the patient's first negative peripheral blood culture. For multilumen catheters, a minimum 2-hour dwell time was maintained for each lumen. Organism-specific systemic antimicrobials were continued for the duration of the ETL. Blood cultures through each catheter lumen were obtained 72 hour after first negative peripheral culture and at least 72 hour after therapy was concluded. If either of the 2 cultures were positive, ELT was considered to have failed and the catheter was removed. Ethanol lock therapy side effects were sought by reviewing all encounters between study subjects and the healthcare system for a 2-month period after ELT.

RESULTS

During the course of this study, 15 patients were enrolled. The patients ranged from 4 months of age to 17 years old, with a majority of them being less than 2 years of age (10 of 15; Table 1). Among the 15 children, 8 were male. Seven of the patients were *total parenteral nutrition* dependent due to intestinal failure and 5 were immune-compromised. Thirteen of the 15 catheters were Broviac catheters. There were 7 single lumen, 7 double lumen, and 1 triple lumen catheter (Table 1). Twenty-one organisms were identified from the 15 patients, 12 bacteria and 9 fungi. There were 7 pure bacterial infections, 4 fungal infections, and 4 mixed bacterial and fungal infections (Table 2). Seven of the 11 bacterial isolates were Gram-positive organisms with *Enterococcus* accounting for 4 of the 7 Gram-positive infections. *Candida* species accounted for 8 of the 9 fungal infections with *Candida albicans* being the predominant species isolate.

The overall salvage rate in the study was 86.7% (13 of 15). Similar salvage rates were achieved with bacterial (10 of 12; 85.7%), fungal (4 of 4; 100%), or mixed catheter infections (3 of 4; 75%). Eighty-eight percent of the Gram-positive isolates (7 of 8), 75% of the Gram-negative isolates (3 of 4), and 88% of the fungal (7 of 8) isolates were eliminated (Table 2). All bacteria cleared using ethanol locks had previously failed appropriate therapy before enrolling in the study, and fungal isolates were highly resistant to standard antimicrobial strategies. Study

Table 1. Study Subjects' Basic Demographic Information, Infectious Organism, Catheter Type and Study Outcomes*

Patient No.	Age	Sex	Underlying Condition	Organism	Catheter (Lumen)	Treatment Success
1	17 years	F	IF	*Klebsiella pneumoniae*	Broviac (2)	Yes
2	4 months	M	IF	*Serratia marcescens, Candida lusitanaie, Candida parapsilosis*	Broviac (1)	No
3	8 years	F	ESRD	*Enterobacter cloacae*	Broviac (1)	Yes
4	7 months	F	IF	*Candida albicans*	Broviac (3)	Yes
5	8 years	M	Atax-telagectasis	*Cryptococcus neoformans*	Port (2)	Yes
6	12 months	M	SCID	CNS	Broviac (2)	No
7	11 months	M	IF	CNS	Broviac (1)	Yes
8	4 years	F	Liver transplant endocarditis	MRSA	Port (2)	Yes
9	16 months	F	Neuroblastoma	*C albicans Enterococcus faecium* CNS	Broviac (2)	Yes
10	5 months	M	IF	*E faecalis*	Broviac (1)	Yes
11	6 months	F	IF	*C albicans, E fecalis*	Broviac (1)	Yes
12	2 years	M	Hepatoblastoma	*E faecalis*	Broviac (2)	Yes
13	9 months	M	Pulmonary hypoplasia	*C albican, S marcescens*	Broviac (1)	Yes
14	5 years	M	CHD	*C albicans*	Broviac (2)	Yes
15	8 months	F	IF	*C parapsilosis*	Broviac (1)	Yes
				Type of Infection	No. (Success)	Salvage Rate
				Bacterial	7 (6)	85.7%
				Mixed (bacterial and fungal)	4 (3)	75.0%
				Fungal	4 (4)	100%
				Gram positives	8 (7)	87.5
				Gram negatives	4 (3)	75%

Abbreviations: CHD, congenital heart defect; CNS, central nervous system; ESRD, *end-stage renal disease*; IF, intestinal failure; MRSA, *methicillin-resistant Staphylococcus aureus*; SCID, severe combined immunodeficiency.

*Bottom of the table shows infectious organisms along with outcomes. Note the significant salvage rate across all type of infectious organism, including fungal infections.

Table 2. Infectious Organisms Along With Outcomes Are Presented*

Salvage Rates by Infection Characteristics			
Type of Infection	No. (Success)	Salvage Rate	*P*
Bacterial	7 (6)	85.7%	.0001
Mixed (bacterial and fungal)	4 (3)	75.0%	.01
Fungal	4 (4)	100%	.0001
Gram positives	8 (7)	87.5	.0001
Gram negatives	4 (3)	75%	.01
Total	15 (13)	86.7%	.0001

*Note the significant salvage rate across all type of infectious organism, including fungal infections.

subjects were monitored for 2 months after ELT via medical records; none of the cases with negative blood cultures at 72 hours posttherapy completion relapsed with the same organism during the 2-month period. No side effects were reported in the study.

DISCUSSION

Ethanol locks have been shown to be an effective supplement to systemic antibiotics for the management of bacterial catheter infections [8]. An ETL salvage protocol was initiated at the University of Michigan for infected catheters, the immediate removal of which was not deemed to be in the patient's best clinical interest by their primary team. The first 3 patients enrolled in the study were either critically ill or had persistent fungemia associated with a fungal catheter infection. These 3 patients were successfully treated with a combination of systemic antifungal and ELT, and this treatment was previously reported in a small case report [14]. Since the initial report, an additional 12 patients have been enrolled, 9 of whom have been successfully managed using ELT following failure of standard treatment. Success to date does not appear to be organism dependent.

Fungal catheter infections are far more complicated not only because of the remarkably low cure rates using standard therapy, but a previous study in neonates suggested that early catheter removal, within the first 3 days, decreased mortality rates [16, 17]. In fact, 7 of the 8 catheters infected with fungi were successfully treated, and catheter removal was not required.

Although the overall salvage rate in this study was 86.7%, it needs to be stressed that these rates were in patients who had already failed standard treatment. Of the 12 bacteria and 9 fungi isolated, 11 (92%) and 8 (88%) of them, respectively, were treated effectively without growth on subsequent cultures. This high rate of successful clearance suggests a remarkable potential for ELT as adjunctive treatment to standard antibiotics. Although our study did not reveal any side effects, the ELT literature identifies side effects such as increase thrombotic risks that need to be considered when weighing the use of ELT. Further studies need to be performed to better understand the side effects of ELT [18].

The advantages of this study should be tempered with the potential downsides. First, the utilization of ELT salvage may well have led to a longer in-hospital stay for many children relative to line removal, which may have led to a faster resolution of intensive care. However, because a period of infection-free status and operative placement of a new CVAD would be needed, this prolongation of in-hospital stay is not clear. In addition, the economic advantages of this approach will need to be explored with future studies. Although the mean cost of therapy with ELT salvage resulted in potentially avoiding both operative procedures for line removal and line placement, the potentially increased hospitalization rates may neutralize any economic benefit.

The study has some limitations that need to be considered. Given that the study subjects were not recruited consecutively or from 1 clinic, it was difficult to identify a full cohort of patients at risk to measure the impact of the intervention. The absence of a control group limits the generalizability of our findings. Furthermore, confirmation of catheter relatedness was difficult. Both of these limitations hinder the generalization of the findings and highlight the need for future research on ELT to best understand its potential clinical role.

Previous studies have demonstrated the effectiveness of ethanol lock treatment. Dannenberg et al [19] demonstrated the effective use of adjuvant ELT with standard systemic antibiotics in oncologic patients. Onland et al [8] demonstrated the effective use of ELT in conjunction with systemic antibiotics in the pediatric population. Only 1 patient in Onland et al's [8] study had a fungal infection. To our knowledge, this is the first study to demonstrate the effective use of adjuvant ELT in patients who have failed standardized therapy who are infected with bacterial or fungal organisms.

CONCLUSIONS

Given the limited research on ELT, more studies are needed before ELT can be safely recommended for clinical use outside of a research context. Ethanol lock therapy salvage is a potentially viable approach for bacterial, fungal, as well as mixed CVAD infections that have failed conventional antimicrobial

therapy. Future prospective randomized trials are strongly warranted to definitively demonstrate the use of this approach.

Notes

Financial support. This work was funded by Blue Cross Blue Shield of Michigan.

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

References

1. Maki DG, Kluger DM, Crnich CJ. The risk of bloodstream infection in adults with different intravascular devices: a systematic review of 200 published prospective studies. Mayo Clin Proc **2006**; 81:1159–71.
2. Zack J. Zeroing in on zero tolerance for central line-associated bacteremia. Am J Infect Control **2008**; 36:S176.e1–2.
3. O'Grady NP, Alexander M, Burns LA, et al. Guidelines for the prevention of intravascular catheter-related infections. Am J Infect Control **2011**; 39:S1–34.
4. Opilla MT, Kirby DF, Edmond MB. Use of ethanol lock therapy to reduce the incidence of catheter-related bloodstream infections in home parenteral nutrition patients. JPEN J Parenter Enteral Nutr **2007**; 31:302–5.
5. Sanders J, Pithie A, Ganly P, et al. A prospective double-blind randomized trial comparing intraluminal ethanol with heparinized saline for the prevention of catheter-associated bloodstream infection in immunosuppressed haematology patients. J Antimicrob Chemother **2008**; 62:809–15.
6. Jones BA, Hull MA, Richardson DS, et al. Efficacy of ethanol locks in reducing central venous catheter infections in pediatric patients with intestinal failure. J Pediatr Surg **2010**; 45:1287–93.
7. Kim EY, Saunders P, Yousefzadeh N. Usefulness of anti-infective lock solutions for catheter-related bloodstream infections. Mt Sinai J Med **2010**; 77:549–58.
8. Onland W, Shin CE, Fustar S, et al. Ethanol-lock technique for persistent bacteremia of long-term intravascular devices in pediatric patients. Arch Pediatr Adolesc Med **2006**; 160:1049–53.
9. Broom J, Woods M, Allworth A, et al. Ethanol lock therapy to treat tunnelled central venous catheter-associated blood stream infections: results from a prospective trial. Scand J Infect Dis **2008**; 40:399–406.
10. Mouw E, Chessman K, Lesher A, Tagge E. Use of an ethanol lock to prevent catheter-related infections in children with short bowel syndrome. J Pediatr Surg **2008**; 43:1025–9.
11. Cober MP, Kovacevich DS, Teitelbaum DH. Ethanol-lock therapy for the prevention of central venous access device infections in pediatric patients with intestinal failure. JPEN J Parenter Enteral Nutr **2011**; 35:67–73.
12. O'Grady NP, Alexander M, Dellinger EP, et al. Guidelines for the prevention of intravascular catheter-related infections. Centers for Disease Control and Prevention. MMWR Recomm Rep **2002**; 51:1–29.
13. Bouza E, Burillo A, Munoz P. Catheter-related infections: diagnosis and intravascular treatment. Clin Microbiol Infect **2002**; 8:265–74.
14. Blackwood RA, Klein K, Micel L, et al. Ethanol locks therapy for resolution of fungal catheter infections. Pediatr Infect Dis J **2011**; 30:1105–7.
15. Mermel A, Allon M, Bouza E, Craven D, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 Update by the Infectious Diseases Society of America. Clin Infect Dis **2009**; 49:1–45.
16. Karlowicz MG, Hashimoto L, Kelly R, Buescher ES. Should central venous catheters be removed as soon as candidemia is detected in neonates? Pediatrics **2000**; 106:E63.
17. Goudie A. Attributable cost and length of stay for central line-associated bloodstream infections. Pediatrics **2014**; 133:e1525–32.
18. Mermel L. Adverse effects associated with ethanol catheter lock solutions: a systematic review. J Antimicrob Chemother **2014**; 69:2611–9.
19. Dannenberg CC. Ethanol-lock technique in the treatment of bloodstream infections in pediatric oncology patients with broviac catheter. J Pediatr Hematol Oncol **2003–2008**; 25:616.